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the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The Examiner acknowledges that the specification is enabling for antisense compound that inhibit expression of phosphatidylinositol-4-phosphate 5-kinase I α *in vitro*. Yet the Examiner suggests that the specification as filed is not enabling for *in vivo* uses of the claimed antisense compounds. The Examiner cites several articles on the technology of antisense to support the position regarding extrapolation to *in vivo* and pharmaceutical uses. Applicants respectfully traverse this rejection of the claims.

Applicants disagree with the Examiner's suggestion that cited references support the position that application of antisense *in vivo* as a pharmaceutical is unpredictable.

The Examiner has pointed to two articles on the technology of antisense oligonucleotides to support the view that antisense technology is unpredictable. However, when one reads each of these papers as a whole, as required under MPEP 2141.02, these references actually teach the potential usefulness of this class of drugs in humans, and more importantly fail to provide any reasonable basis to doubt the pharmacological activity observed

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in cells in the instant invention would also occur in cells in animals and humans.

The paper by Jen and Gewirtz (2000) is a review paper on the evolution of technology to suppress gene expression, including antisense technology, and its use in human disease. Nowhere does this paper teach or suggest that antisense compounds identified from well-designed *in vitro* studies would be inherently unpredictable when used *in vivo*.

The paper by Branch (1998) teaches the need to develop antisense molecules based on sound data and careful screening, such as is presented in the instant specification. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

However, in an earnest effort to advance the prosecution of this case, Applicants have amended claim 15 and canceled claims 16-18, with Applicants reserving the right to file a continuing application directed to this subject matter. Therefore, withdrawal of the rejection is requested in light of these amendments.

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II. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 1, 2, 4-14, 19 and 20 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Honda et al. (1999), Loijens et al. (1996), and further in view of Weintraub (1990), Baracchini et al. (US Patent 5,801,154), and Fritz et al. (1997). The Examiner suggests it would have been *prima facie* obvious for one of ordinary skill to be motivated to make antisense oligonucleotides as claimed because the cited art teaches a physiological role for the protein in membrane ruffle formation and regulation of signal transduction, while Loijens et al. teach the variants claimed as being derived from phosphatidylinositol-4-phosphate 5-kinase, $\text{I}\alpha$. The Examiner suggests it would have been obvious then to make antisense oligonucleotides encoding phosphatidylinositol-4-phosphate 5-kinase, $\text{I}\alpha$ since Weintraub teach antisense nucleic acids can selectively inhibit the activity of genes and gene expression. The Examiner then suggests that one of skill would have a reasonable expectation of success in modifying antisense compounds as claimed based on the teachings of Baracchini and Fritz. Applicants respectfully disagree with the Examiner's conclusions.

Honda et al. (1999) disclose only the biological role of phosphatidylinositol-4-phosphate 5-kinase, $\text{I}\alpha$ as a downstream

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effector of small G protein ARF6 in membrane ruffle formation. Nowhere does this reference teach or suggest use of antisense compounds of any type to target the phosphatidylinositol-4-phosphate 5-kinase, I α gene and to inhibit its expression using antisense.

Loijens et al. (1996) disclose the peptide sequence of phosphatidylinositol-4-phosphate 5-kinase, I α isolated from bovine erythrocytes and then the full-length cDNA coding phosphatidylinositol-4-phosphate 5-kinase, I α and two predicted splice variants that were cloned from a human fetal brain cDNA library. The paper reports the distribution of phosphatidylinositol-4-phosphate 5-kinase, I α in tissues. However, nowhere does this paper teach or suggest antisense compounds of any type targeted to phosphatidylinositol-4-phosphate 5-kinase, I α of SEQ ID NO: 3 as claimed. It is only with the specification in hand that one of skill has evidence that antisense inhibition of phosphatidylinositol-4-phosphate 5-kinase, I α is successful as a method to inhibit expression of this gene, or its splice variants. Therefore, neither of these primary references teach or even suggest use of antisense compounds of any type for inhibition of expression of phosphatidylinositol-4-phosphate 5-kinase, I α or its splice

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variants. The secondary references cited fail to overcome the deficiencies in teaching of these primary references.

Weintraub (1990) is an older paper on the technology of antisense and only discusses the use of antisense as a research tool. Nowhere does this paper teach or suggest antisense compounds of any type targeted to phosphatidylinositol-4-phosphate 5-kinase, I α of SEQ ID NO: 3 as claimed. Additionally, this paper explicitly states at page 46 that "many important refinements of antisense technology are still needed, and many important questions must still be answered..." Thus, one of skill in the art would not understand using this paper that antisense technology would be successfully used to inhibit expression of any gene, without evidence of such use.

The '154 patent teaches modification to antisense oligonucleotides in general as a way to enhance activity. However, this general discussion of modified oligonucleotides does not teach or suggest use of antisense compounds of any type to target a specific gene, phosphatidylinositol-4-phosphate 5-kinase, I α , and the successful inhibition of expression using antisense.

Fritz et al. (1997) is a paper that describes carrier systems for antisense oligonucleotides, in general terms.

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Nowhere does this paper teach or suggest antisense compounds of any type targeted to phosphatidylinositol-4-phosphate 5-kinase, I α of SEQ ID NO: 3 as claimed.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Mere teaching of the function of a gene and/or its protein product and then teaching of antisense technology in general does not provide one of skill with the expectation of success in developing antisense targeted to a specific gene. The limitations of the claims as filed, which specify antisense compounds targeted to phosphatidylinositol-4-phosphate 5-kinase, I α of SEQ ID NO: 3, or variant thereof, are not taught or even suggested by any of the references individually or when combined. Therefore, the limitations of the claims as amended clearly are not taught or suggested by the combination of prior art references, nor is any expectation of successful use of such antisense compounds provided by the combination of prior art. It

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is only with the specification in hand that one of skill would understand that antisense compounds targeted to phosphatidylinositol-4-phosphate 5-kinase, I α or one of its variants could be used to inhibit expression of this gene. Thus, the combination of prior art cited cannot render the instant claimed invention obvious. Withdrawal of this rejection is therefore respectfully requested.

III. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Respectfully submitted,

Jane Massey Licata

Jane Massey Licata
Registration No. 32,257

Date: December 3, 2002
LICATA & TYRRELL P.C.
66 E. Main Street
Marlton, New Jersey 08053
(856) 810-1515

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 16-18 have been canceled.

Claim 15 has been amended as follows:

15. (amended) A method of inhibiting the expression of phosphatidylinositol-4-phosphate 5-kinase, $I\alpha$ in cells or tissues comprising contacting said cells or tissues in vitro with the compound of claim 1 so that expression of phosphatidylinositol-4-phosphate 5-kinase, $I\alpha$ is inhibited.